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Principles of Analytic Epidemiology

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PREFACE

This handbook has been developed over the past several years as a reference guide for Epidemic Intelligence Service (EIS) officers and for use by persons taking the EIS course in epidemiology given each summer at the Centers for Disease Control. We welcome comments and suggestions about its contents.

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PRINCIPLES OF ANALYTIC EPIDEMIOLOGY

A. INTRODUCTION

DIFFERENCES BETWEEN CHRONIC AND ACUTE DISEASE EPIDEMIOLOGY

The principles and methods of analytic epidemiology are applicable to all types of disease, whether acute or chronic, infectious or noninfectious. They are most often associated, however, with studies of chronic disease. This reflects differences between chronic and acute disease in terms of 1) duration of latency (time interval between cause and effect), 2) magnitude of incidence, and 3) complexity of causation:

	Chronic disease	Acute disease
Latency	long, variable, or obscure	short
Incidence	usually low (less than 1%)	usually high in exposed populations
Causation	usually multi-factorial with no one cause dominant	single causes often dominant

Under conditions of short latency, high incidence, and simple causation, cause and effect in acute disease can often be linked directly through descriptive epidemiologic data or through short-term cross-sectional analyses. For chronic diseases, however, relatively elaborate cohort* and case-control studies are often required because of long latency, low incidence, and complex causation.

REFERENCES

1. MacMahon B, Pugh TF: Epidemiology: Principles and Methods. Little, Brown and Co., Boston, 1970, pp 39-46, 207-282.

2. Lilienfeld AM, Foundations of Epidemiology. Oxford University Press, New York, 1976.

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* In the context of epidemiologic studies, the word "cohort" denotes a group of persons exposed or not exposed to a given risk factor.

DIFFERENCES BETWEEN COHORT AND CASE-CONTROL STUDIES

Although both cohort and case-control studies measure associations between risk factors and disease, their approaches are fundamentally different: cohort studies measure <u>frequencies of disease occurrence</u> among persons exposed to different levels of risk, while case-control studies measure <u>frequencies of risk factor exposure</u> among persons with and without disease. Illustrative examples of cohort and case-control studies are given in Appendices I, II and III.

<u>Cohort study</u>

Compares frequency of disease among persons exposed to risk factor to frequency among persons not exposed

Risk factor	Disease yes	Disease no	Total
yes	A	B	A+B
no	C	D	C+D

$\frac{A}{A+B}$ compared to $\frac{C}{C+D}$

<u>Case-control study</u>

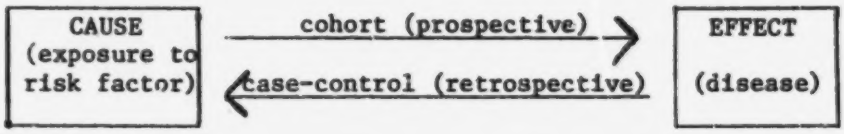
Compares frequency of risk factor exposure among persons with disease to frequency among non-disease controls

Risk factor	Disease yes	Disease no
yes	a	b
no	c	d
Total	a+c	b+d

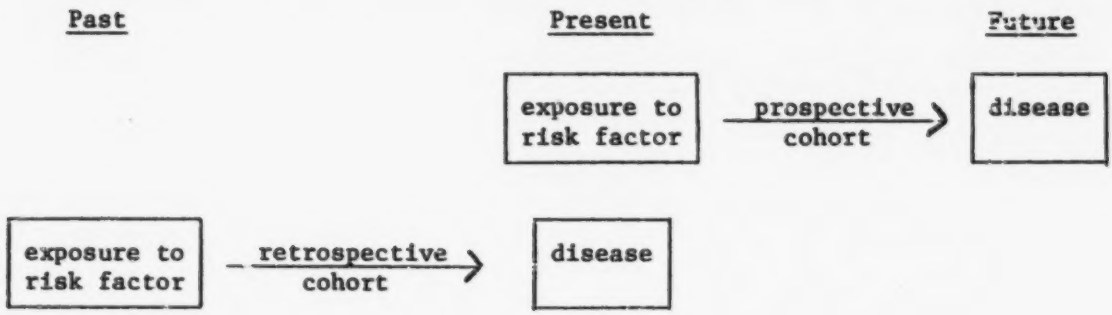
$\frac{a}{a+c}$ compared to $\frac{b}{b+d}$

By convention the capital letters (A,B,C,D) designate study populations defined by risk exposure and disease occurrence. The small letters (a,b,c,d) represent samples of populations, usually of unknown and differing sampling frequencies. Capital letters are therefore used to describe cohort study dynamics which involve calculating rates of disease frequency in defined populations. Small letters, however, refer to case-control studies where sampling underlies the selection of cases and controls.

The terms "prospective" and "retrospective" are commonly used in relation to cohort and case-control studies, "prospective" equated with cohort and "retrospective" with case-control. This implies that cohort studies move forward from risk factor to disease, from cause to effect, by first identifying populations exposed and not exposed to risk factor and then measuring disease frequencies among them. Case-control studies, however, move backward from disease to risk factor, from effect to cause, by first identifying persons with and without disease and then measuring degrees of exposure to risk factor.



Occasionally the terms "prospective" and "retrospective" are used in a temporal rather than a conceptual sense. Thus a cohort study which measures current disease frequency among populations exposed to risk factors in the past is commonly called a "retrospective" cohort study.



Both cohort and case-control studies have relative advantages and disadvantages in terms of avoidance of bias and ease of execution. Traditionally, cohort studies are considered less biased than case-control studies since they avoid the subjectivity involved in collecting after-the-fact exposure data from persons already affected by disease. However, while case-control studies may involve more bias in determining risk exposure, cohort studies may involve more bias in determining disease occurrence; both are open to bias if groups under comparison are not comparable.

Case-control studies are generally easier, quicker, and less expensive to carry out than cohort studies. Most cohort studies entail observation of large numbers of persons who in the case of prospective cohort studies must be followed over long periods of time. Retrospective cohort studies, on the other hand, involve no such time delay. Because of expense and time, prospective cohort studies are usually not attempted until after case-control studies have first been done.

B. SELECTION OF GROUPS TO BE STUDIED

The first step in conducting a cohort or case-control study is the selection of groups to be studied. Six factors are important in this process: 1) comparability of groups, 2) risk factor frequency, 3) disease frequency, 4) degree of study sensitivity desired, 5) degree of representativeness desired, and 6) accessibility of population groups for study.

COMPARABILITY

To assure that groups under study are comparable, it is of prime importance to avoid selection bias as subjects or populations are chosen. Whatever comparisons are made, comparison groups should be as similar to one another as possible in all respects other than the risk factor under study. If matching is used to achieve comparability between groups, matching should involve only potential confounding variables, i.e., variables related both to disease and to risk factor. To actually confound, of course, a variable must fulfill each of the following 2 criteria: 1) it must be related both to frequency of risk exposure and to frequency of disease recognition; 2) it must occur with differing frequencies in groups being compared (cohorts or cases and controls). Matching for non-confounding variables ("overmatching") or matching for confounding variables that nonetheless are associated with the actual risk-factor/disease causal chain can obscure risk factor/disease associations.

FREQUENCY OF RISK FACTOR EXPOSURE

For cohort studies, if the risk factor exposure under study is relatively common (cf. cigarette smoking or use of contraceptive pills), the exposed cohort can be drawn by sampling from the general population; if uncommon, special high-risk groups must be sought (cf. occupational groups with respect to industrial risk exposures). Non-exposed or low-exposure comparison groups can involve 1) rates of disease in the general population, 2) special cohorts particularly selected on the basis of low exposure to risk factor, or 3) internal comparisons within the exposed cohort whereby comparisons are made by degree of risk factor exposure.

For case-control studies, frequency of risk factor exposure is a major influence in determining how many cases should be studied and how many controls. If cases are drawn from a defined population, the total population can be used as controls, provided frequency of risk factor exposure can be measured. More commonly, controls represent a sample of an undefined population, whether selected on a matched or an unmatched basis.

DISEASE FREQUENCY

For cohort studies, the rarer the disease, the larger the cohort may need to be or the longer it will have to be followed. Use of high-risk cohorts may increase expected frequency of disease, and hence permit use of smaller cohorts or shorter follow-up periods. For case-control studies, disease frequency is not a crucial factor.

DEGREE OF STUDY SENSITIVITY

Determination of sample size involves simultaneous consideration of risk factor frequency, disease frequency, and desired degree of study sensitivity. If one wishes to detect a slight increase in risk with great precision, comparison groups (cohorts or cases and controls) will need to be larger than for less precise detection of large risk increases.

REPRESENTATIVENESS

Generally, it is hoped that the results of cohort and case-control analyses will represent the state of affairs in the general population in terms of disease causation. One should be aware, however, of the extent to which comparison groups may or may not be representative of the general population or of all cases of a given disease. Studies drawn from special groups such as hospital patients or particular occupation groups may, for various reasons, not be suitable for extrapolation to other populations or to the population-at-large.

ACCESSIBILITY

Whatever comparison groups are selected must be accessible for study, with practical means available for collection of data concerning risk exposure and disease occurrence. To these ends, both cohort and case-control studies often focus on such groups as obstetric populations, prepaid medical groups, or geographically confined populations, making particular use of such convenient data sources as hospital records and death certificates.

C. COLLECTION OF DATA

COMPARABILITY

During the second phase of an analytic study, when data are collected concerning risk factor exposure or disease occurrence, it is crucial to maintain comparability of data collection methods and thus minimize ascertainment bias. Whatever sources and methods are used (medical records, questionnaires, direct patient examinations, vital records), uniformity is essential. Variations in data collection (cf. non-response to questionnaires) should be assessed for discrepancies between groups being compared. If bias affects any or all groups, comparisons may be distorted or confounded.

VALIDITY

Questions of validity must also be considered. To what extent do data collected concerning risk factor exposure and disease occurrence reflect the truth? In cohort studies, for example, how often are exposed persons included in the risk-free cohort? (false negatives: how "sensitive" is the study?); and conversely, how often are risk-free persons recorded as exposed? (false positives: how "specific" is the study?)

Alternatively, from the table below one can define sensitivity as representing ability to detect true positives (ascertained positive/true positive) and specificity as representing/ability to detect true negatives (ascertained negative/true negative).

Actual exposure or disease	Ascertained exposure or disease	
	positive	negative
positive	true positive	false negative
negative	false positive	true negative

D. ANALYSIS OF DATA

The third and final component of a study consists of data analysis. This process involves three major components: 1) further adjustments to achieve comparability between cohorts or between cases and controls; 2) measurements of risk by which rates of disease in exposed and non-exposed populations are compared, and 3) techniques by which causality may or may not be inferred from observed associations between risk factor exposure and disease.

COMPARABILITY

When matching techniques are not used in the process of collecting data, the effects of potential confounding variables can be weighed by stratification of data during analysis. Comparison groups (cohorts or cases and controls) are "stratified" into sub-groups with respect to variables suspected of actual confounding (cf. age). Frequencies of disease or risk factor exposure are then compared between sub-groups or strata. If relative frequencies (and hence values of relative risk) differ from group to group, variables may be considered confounding (see Appendix III, page 16, for a theoretical example).

In cohort studies, where duration of risk exposure may vary among cohorts, comparability of disease rates is commonly achieved by estimation of person-years at risk (a procedure resembling life-table construction) followed by calculation of age-adjusted or age-standardized rates. Estimates of person-years at risk allow for changes in cohort size over time (cohort members enter the cohort at different times and ages, become lost to follow-up, or die) and for increases in age if age is an important variable for a given study. Calculation of age-standardized rates (whether by direct or indirect methods) eliminates the confounding effect of differing age distributions in comparison groups by adjusting rates to some standard reference.

MEASURES OF RISK

Two measures of risk are commonly used:

1) Relative risk or the ratio of disease rate in exposed persons to rate in non-exposed:

$$\frac{A}{A+B} \text{ divided by } \frac{C}{C+D}$$

2) Attributable risk or the difference between disease rate in exposed persons (or in the total population) and rate in non-exposed:

$$\frac{A}{A+B} \text{ minus } \frac{C}{C+D}$$

Relative risk (a ratio) assesses the strength of associations between risk factor and disease, while attributable risk (a rate) measures the rate of disease attributable to the particular risk factor. Attributable risk can be translated into attributable risk percent by dividing attributable risk (A/A+B - C/C+D) either by the total disease rate in the exposed population (A/A+B) (percent of disease in the exposed population attributable to the risk factor) or by the total disease rate in the entire population, exposed and unexposed combined (A+C/A+B+C+D) (percent of disease in the total population attributable to the risk factor). The latter value is dependent on the frequency of risk factor exposure in the total population.

In interpreting values of either relative or attributable risk, one must distinguish between the size of the risk value and its statistical significance. Depending on sample size, frequency of disease, and frequency of risk factor exposure, high values may be statistically insignificant (small sample size), while low values may be statistically significant (large sample size).

In cohort studies, calculation of relative and attributable risk values merely involves direct division and subtraction of rates. Case-control studies, however, do not usually permit direct measurement of disease rates, but merely measurement of frequencies of risk factor exposure. (The one exception involves the special circumstance where cases in a case-control study encompass either all cases or a known sample of all cases in a defined population; provided controls are from the same population and provided their sampling frequency is also known, disease rates can be derived, allowing values of relative and attributable risk to be estimated directly.)

RELATIVE RISK IN UNMATCHED CASE-CONTROL STUDY

Two different procedures are used for calculating relative risk in case-control settings, one for situations where controls are selected by matching, and the other for situations where controls are unmatched. In the unmatched setting, relative risk is calculated by the following formula:

$$\text{Relative risk} = \frac{ad}{bc}$$

This formula, the ratio of cross-products in the standard 4-way table (see page 2), is derived under the following logic (an hypothetical illustration is provided in Appendix IV):

> Since cases of disease in most chronic disease studies represent only a small fraction of exposed and non-exposed populations, B is about equal to A+B and D to C+D. The formula for relative risk can therefore be simplified as follows:

$$\text{Relative risk} = \frac{\frac{A}{A+B}}{\frac{C}{C+D}} \longrightarrow \frac{\frac{A}{B}}{\frac{C}{D}} \longrightarrow \frac{AD}{BC}$$

> In the case-control setting, cases and controls represent population samples, a different but unknown sampling frequency for each (x for cases a+c, y for controls b+d). Applied to the simplified formula for relative risk (ad/bc), these frequency terms cancel out, thus permitting the use of the cross-products ratio in case-control analysis.

$$\text{Relative risk} = \frac{axdy}{bycx} = \frac{ad}{bc}$$

ODDS RATIO

The same formula can be derived as an odds ratio by dividing the odds that a case will have been exposed to risk factor (a/c) by the odds that a control will have been exposed (b/d). Thus:

$$\text{Odds ratio} = \frac{\frac{a}{c}}{\frac{b}{d}} = \frac{ad}{bc}$$

RELATIVE RISK IN MATCHED CASE-CONTROL STUDY

If matching is used in selecting controls, the matching (or pairing) should be retained for analytic purposes as shown in the following 4-way table of case-control pairs:

Control exposed to risk factor	Case exposed to risk factor: yes	Case exposed to risk factor: no
yes	e	f
no	g	h

In calculating relative risk, one need consider only discordant case-control pairs, represented by g (case exposed to risk factor, control not) and by f (control exposed to risk factor, case not):

$$\text{Relative risk} = \frac{g}{f}$$

ATTRIBUTABLE RISK PERCENT IN CASE-CONTROL STUDY

The following formulae allow indirect calculation of attributable risk percents in case-control studies, one for populations exposed to risk, the other for total populations, exposed and unexposed combined (P = proportion of population exposed to risk factor, R = relative risk):

$$\text{Attributable risk percent (exposed population)} = \frac{R-1}{R} \times 100$$

$$\text{Attributable risk percent (total population)} = \frac{P(R-1)}{P(R-1)+1} \times 100$$

INFERENCE OF CAUSALITY

The existence of a statistical association between risk factor and disease is not proof of causation; other explanations include associations which are frankly spurious and associations which are indirect by virtue of intermediate or related variables. Although epidemiologic data alone cannot establish causation, various kinds of epidemiologic evidence can provide considerable support for a causal hypothesis. Such data include the strength of the association, its specificity and consistency, and perhaps most importantly dose-response relationships. If increasing exposure to a given risk factor is associated with increasing disease incidence, (i.e., if values of relative risk increase as exposure to risk rises), the likelihood of a causal relationship is greatly enhanced.

APPENDIX I: PROSPECTIVE COHORT STUDY

The Atomic Bomb Casualty Commission follow-up of Japanese exposed to atom bomb irradiation at Hiroshima and Nagasaki in 1945 is a classic example of a prospective cohort study. Starting in 1950, approximately 100,000 survivors were enrolled in the study to be followed throughout their lifetimes with respect to various disease outcomes, particularly cancer and genetic disorders.

Medical data for this cohort are systematically collected on an ongoing basis with thorough review of all available pathologic material for confirmation of diagnoses. In addition, each member of the cohort has been classified as far as possible with respect to extent of exposure to bomb irradiation as determined by distance from the bomb epicenter at time of explosion and by degree of shielding.

One of the early findings concerned increased leukemia incidence among bomb survivors. The following data summarize this disease/risk factor association for cases diagnosed among Hiroshima residents during the 16-year period October 1950 - September 1966.

Irradiation dose (rads)	Exposed Population		Number of cases	Crude annual incidence per 100,000
	Number	Person-years		
under 5	62,515	915,000	27	3.0
5-19	10,541	156,000	8	5.1
20-49	4,555	67,000	14	20.9
50-99	2,611	38,300	7	18.3
100-199	1,652	24,100	10	41.5
200-299	606	9,000	5	55.6
300+	825	12,100	17	140.5
5+	20,790	306,500	61	19.9
Total	83,305	1,221,500	88	7.2

DOSE-RESPONSE

A clear dose-response relationship exists with crude rates rising from 3/100,000 for persons with less than 5 rads exposure to over 140/100,000 for persons exposed to over 300 rads. These data are based on person-years which reflect overall survivorship in the cohort over the 16 years of observation.

RELATIVE RISK

These same data are expressed in terms of relative and attributable risk values in the following table:

Irradiation dose (rads)	Crude annual incidence per 100,000	Relative risk	Attributable risk	
			Rate per 100,000	Percent
under 5	3.0	1.0	0.0	0
5-19	5.1	1.7	2.1	41
20-49	20.9	7.0	17.9	86
50-99	18.3	6.1	15.3	84
100-199	41.5	13.8	38.5	93
200-299	55.6	18.5	52.6	95
300+	160.5	46.8	137.5	98
5+	19.9	6.6	16.9	85
Total	7.2	---	4.2	58

Here, using the under-5 rads group as a reference point, one can see that relative risk of leukemia is increased from 1.7 times for the 5-19 rads group to 46.8 times for the 300+ rads group. Overall risk of leukemia is increased 6.6 times in persons exposed to 5 rads or more, assuming that the under-5 rads risk approximates that in the general unexposed population.

ATTRIBUTABLE RISK

Attributable risks are expressed both as absolute rates and as percents (attributable risk percent) within each risk category. By this scheme, 58% of cases in the entire population can be attributed to bomb irradiation, 90% or more at levels over 20 rads, and virtually all (98%) at the highest dose level.

REFERENCE

Ishimaru T, Hoshino T, Ichimaru M, et al: Leukemia in atomic bomb survivors, Hiroshima and Nagasaki, 1 October 1950 - 30 September 1966. Radiation Research 45:216-233, 1971.

APPENDIX II: RETROSPECTIVE COHORT STUDY

An example of a retrospective cohort investigation is the British study of leukemia mortality among persons x-rayed for ankylosing spondylitis of the spine. The study was conducted in 1955, identifying a cohort of about 13,000 persons given therapeutic doses of x-ray for spondylitis over the 20-year interval 1935-1954. Amounts of x-ray received were quantitated as precisely as possible by review of medical records. Death registration lists were then reviewed for the same time period to identify deaths among members of the cohort. Specific causes of death were recorded and confirmed by review of medical records. Expected numbers of deaths for specific causes of death were calculated by applying age-, race-, sex-, cause-, and year-specific mortality rates for Britain as a whole to numbers of person-years accumulated by members of the cohort over the study period.

VALIDITY - COMPARABILITY

By using existing records from past years, both to define the cohort under study and to assemble disease incidence data, this study represents a temporally "retrospective" cohort approach. By giving particular attention to review of actual medical and radiologic records, the investigators sought to ensure validity of the data. They also sought comparability between mortality in irradiated spondylitics and mortality in the general population, by adjusting rates for age, sex, race, and year of death. While spondylitis itself might represent an uncontrolled confounding variable (i.e., the rheumatoid process per se might predispose to leukemia), the study was unable to test this possibility directly, since very few spondylitics went without x-ray therapy. (However, since the study results showed a strong dose-response relationship between x-ray dose and leukemia incidence, the likelihood of spondylitis being the true causative factor is remote.)

The major finding of the study was that risk of developing leukemia or aplastic anemia was greatly increased among irradiated spondylitics. The following table, limited to confirmed cases recorded on death certificates specifically as leukemia or aplastic anemia, demonstrates this association:

Disease	Number of deaths	
	Observed	Expected
Leukemia	22	2.40
Aplastic anemia	11	0.25

RISK VALUES

From these numbers one can estimate both relative risk and attributable risk values: for leukemia, RR = 22/2.40 = 9.2; AR = 22 - 2.40 = 19.6 cases, or 89% of all observed cases "attributable" to x-ray exposure.

DOSE RESPONSE

Since estimates of x-ray dose were available for many members of the cohort, dose-response relationships could be examined. (This particular analysis was confined to male members of the cohort and to cases of leukemia only; living as well as deceased cases were included.):

Mean x-ray dose (rads) to spinal marrow	Persons x-rayed	Person-years at risk after x-ray	Cases of leukemia	Adjusted annual incidence per 100,000
0	-	-	-	4.9
1-499	2,861	18,523	4	19.8
500-999	4,180	21,780	10	46.6
1,000-1,499	3,062	15,730	11	72.1
1,500-2,249	977	4,926	6	144.4
2,250+	207	943	6	721.6
All Doses	11,287	61,902	37	59.8

From these data, a clear dose-response relationship is apparent, rates rising steadily from a non-irradiated baseline level of 4.9/100,000 to over 700/100,000 for heavily irradiated persons. When expressed in terms of relative and attributable risk, these numbers translate as follows:

Mean x-ray dose (rads) to spinal marrow	Adjusted annual incidence per 100,000	Relative risk	Attributable risk	
			Rate per 100,000	Percent
0	4.9	1.0	0	0
1-499	19.8	4.0	14.9	75
500-999	46.6	9.5	41.7	89
1,000-1,499	72.1	14.7	67.2	93
1,500-2,249	144.4	29.5	139.5	97
2,250+	721.6	147.3	716.7	99
All doses	59.8	12.2	54.9	92

Overall relative risk is 12.2, rising from 4.0 to 147.3 as x-ray dose increases. Attributable risk values rise accordingly; overall, 92% of irradiated cases can be attributed to therapeutic x-ray.

REFERENCE

Court Brown WM, Doll R: Leukaemia and Aplastic Anaemia in Patients Irradiated for Ankylosing Spondylitis. Med Res Council Spec Res Ser (London, No. 295, Her Majesty's Stationery Office, 1957).

APPENDIX III: CASE-CONTROL STUDY

An example of a case-control study is the Oxford Survey of Childhood Cancers. Begun in 1955, this project encompasses potentially all children in Britain with cancer since 1953; 8,513 such cases (70% of all cases) were enrolled through 1967. For each case, a healthy control is selected from local birth registration lists, matched by age, sex, and region of residence. Data concerning each case and control are obtained by interviewing mothers and by reviewing available medical records. Prime attention is paid to prenatal events as potential oncogenic risk factors and, in particular, maternal exposure to diagnostic irradiation during gestation.

SELECTION OF CASES AND CONTROLS

Since the individual risk factors under consideration are relatively rare, a large case-control series is desirable with sensitivity increasing as the series grows. Since the diseases under study are also rare, a multi-center or national approach is necessary. Both cases and controls may be considered representative of British children in general to the extent that the 30% of cases not enrolled in the study may resemble the 70% enrolled.

COLLECTION OF DATA

Individual case-control matching ensures reasonable comparability for matched variables (age, sex, place of residence); for other variables, comparability can be tested during data analysis by data stratification. In terms of interview data, however, cases and controls may not be entirely comparable since heightened maternal concern may cause mothers of cases to have stronger recall of prenatal events than mothers of controls. The fact that controls are alive at time of interview while cases are often dead may further influence maternal recall. The validity of collected data, at least as concerns case diagnosis and prenatal x-ray, is fairly well ensured through systematic review of medical records.

Soon after the study began, an association became apparent between prenatal abdominal x-ray and subsequent childhood cancer. For data through 1967, this association has remained unchanged, expressed as follows in terms of both unmatched and matched-pair relative risk:

UNMATCHED RELATIVE RISK

Maternal x-ray during pregnancy	Cases of childhood cancer	Healthy controls
Yes	1,181	840
No	7,332	7,673
Total	8,513	8,513

$$\text{Relative risk} = \frac{1181 \times 7673}{840 \times 7332} = 1.47$$

MATCHED PAIR RELATIVE RISK

Control x-rayed	Case x-rayed: Yes	Case x-rayed: No	Total
Yes	140	700	840
No	1041	6632	7673
Total	1181	7332	8513

$$\text{Relative risk} = \frac{1041}{700} = 1.49$$

STRATIFICATION OF DATA

While cases and controls, by virtue of matching, are comparable in terms of age, sex, and residential locale, differences with respect to other potential confounding variables (cf. birth order, maternal age, socioeconomic class, maternal illness) may contribute to the apparent association between gestational x-ray and childhood cancer. To evaluate such confounding effects, the data can be stratified by presence or absence of particular variables and then analyzed within strata.

THEORETICAL EXAMPLE OF CONFOUNDING

For example, socioeconomic class may independently influence both cancer incidence and frequency of diagnostic x-ray (the higher the social class, the more likely cancer is to be diagnosed and the more likely diagnostic x-ray is to be given). Were there a different socioeconomic gradient among cases than among controls, the apparent overall association between x-ray and cancer might in fact merely represent the confounding effect of socioeconomic differences. If 90% of cases were of high social class and 90% of controls of low social class, relatively weak or nonexistent associations between x-ray and cancer would be found for each social stratum (relative risk 1.26 for high, 0.98 for low) but a relatively strong association overall (relative risk 1.47).

	Social class					
	High		Low		Total	
X-rayed	Cases	Controls	Cases	Controls	Cases	Controls
Yes	1,100	100	81	740	1,181	840
No	6,562	751	770	6,922	7,332	7,673
Total	7,662	851	851	7,662	8,513	8,513
Relative risk	$\frac{1100 \times 751}{100 \times 6562}$		$\frac{81 \times 6922}{740 \times 770}$		$\frac{1181 \times 7673}{840 \times 7332}$	
	= 1.26		= 0.98		= 1.47	

In actual fact, no confounding by social class was found, cases and controls being quite comparable with respect to socioeconomic status. Accordingly, relative risk values in individual social strata correspond closely with overall relative risk:

	Social class					
	High		Low		Total	
X-rayed	Cases	Controls	Cases	Controls	Cases	Controls
Yes	252	161	929	679	1,181	840
No	1,353	1,289	5,979	6,384	7,332	7,673
Total	1,605	1,450	6,908	7,063	8,513	8,513
Relative risk	$\frac{252 \times 1289}{161 \times 1353}$		$\frac{929 \times 6384}{679 \times 5979}$		$\frac{1181 \times 7673}{840 \times 7332}$	
	= 1.49		= 1.46		= 1.47	

INFERENCE OF CAUSALITY

Whether the association between x-ray and cancer represents cause-and-effect is difficult to establish and actually is not yet entirely settled. The potential differences between cases and controls in terms of maternal recall may account to some extent for the study's results. However, similar associations between gestational x-ray and later childhood cancer have been found elsewhere; such findings, together with the concept's general biologic plausibility and its agreement with other epidemiologic and experimental data, support the idea of cause-and-effect.

DOSE-RESPONSE

Further support comes from the data themselves which suggest a dose-response relationship, relative risk values increasing with increasing numbers of x-ray film exposures:

Number of films	Cases	Controls	Relative risk
0	7332	7673	1.00
1	287	239	1.26
2	199	154	1.35
3	96	65	1.55
4	59	28	2.21
5+	65	29	2.35
Unknown number	475	325	1.53
Total x-rayed	1181	840	1.47
Total	8513	8513	

ATTRIBUTABLE RISK PERCENT

Overall attributable risk percent for childhood cancer in relation to gestational x-ray can be indirectly calculated as follows:

$$\text{Attributable risk percent (total population)} = \frac{0.099(1.47-1)}{0.099(1.47-1)+1} = 0.044 \times 100 = 4.4\%$$

This risk value implies that, based on data from the Oxford study, 4.4% of childhood cancers in the general population are attributable to diagnostic x-ray exposure during gestation. For the exposed population, children irradiated in utero, 32% can be attributed to x-ray: (1.47-1)/1.47 = 0.32x100=32%.

REFERENCE

Bithell JF, Stewart AM: Prenatal irradiation and childhood malignancy: a review of British data from the Oxford survey. Brit J Cancer 31:271-287, 1975.

APPENDIX IV: HYPOTHETICAL ILLUSTRATION OF RELATIVE RISK

Consider the following hypothetical situation involving a population or cohort of 100,000 persons, half exposed to risk factor and half not, the frequency of disease being twice as great in exposed as unexposed (relative risk = 2.00):

Risk factor	Disease yes	Disease no	Total
yes	2,000	48,000	50,000
no	1,000	49,000	50,000
Total	3,000	97,000	100,000

$$RR = \frac{A/A+B}{C/C+D} = \frac{2,000/50,000}{1,000/50,000} = 2.00$$

Since 48,000 and 49,000 are each about equal to 50,000, relative risk can be approximated as:

$$RR = \frac{A/B}{C/D} = \frac{2,000/48,000}{1,000/49,000}$$

$$= \frac{AD}{BC} = \frac{2,000x49,000}{1,000x48,000} = 2.04$$

If a case-control study is developed from this population, comparison groups being limited to 1,000 cases (1 in 3 sampling frequency) and 1,000 controls (1 in 97 sampling frequency), the 4-way table might appear as follows:

Risk factor	Disease yes	Disease no
yes	667	495
no	333	505
Total	1,000	1,000
Sampling frequency	x=3	y=97

Using the appropriate sampling frequencies (which cancel out), relative risk can be calculated:

$$RR = \frac{axdy}{bycx} = \frac{(667x3)(505x97)}{(495x97)(333x3)} = \frac{667x505}{495x333} = 2.04$$

It is incorrect to add cases and controls within risk exposure groups. Since sampling frequencies are widely different for cases and controls, the resulting ratio of disease "frequencies" is not a true reflection of relative risk.

Risk factor	Disease yes	Disease no	Total
yes	667	495	1,162
no	333	505	838

$$\frac{667/1,162}{333/838} = 1.44 \neq RR$$